

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

|   |           |   |
|---|-----------|---|
| <p>(51) International Patent Classification <sup>5</sup> :<br/>A61N 1/30</p>  | <p>A1</p> | <p>(11) International Publication Number: WO 93/00959<br/>(43) International Publication Date: 21 January 1993 (21.01.93)</p>   |
| <p>(21) International Application Number: PCT/US92/05587<br/>(22) International Filing Date: 2 July 1992 (02.07.92)<br/>(30) Priority data: 725,279 3 July 1991 (03.07.91) US<br/>(71)(72) Applicant and Inventor: BAER, Bradford, W. [US/US]; 660 Ringwood Avenue, Menlo Park, CA 94025 (US).<br/>(74) Agents: TAUTVYDAS, Daiva, K. et al.; Jones, Askew &amp; Lunsford, 191 Peachtree Street, N.E., 37th Floor, Atlanta, GA 30303-1769 (US).</p>  |           | <p>(81) Designated States: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, PL, RO, RU, SD, SE, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).<br/><br/>Published<br/>With international search report.</p> |
| <p>(54) Title: METHOD AND APPARATUS FOR TREATING TISSUE</p>   |           |   |
|   |           |   |
| <p>(57) Abstract</p> <p>A method of delivering topical drugs to the tissue includes the step of applying the drug to be delivered to one of an area of tissue to be treated and an electrode device (10). The electrode device, which is formed to generate a multiplicity of simultaneous and directionally distinct electrical fields, is then placed in contact with the area of tissue to be treated. Voltage is delivered to the electrode device to generate simultaneous and directionally distinct electric fields at the tissue surface.</p> |           |   |

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

|    |                          |    |  |    |                          |
|----|--------------------------|----|--|----|--------------------------|
| AT | Austria                  | FI | Finland                                  | MI | Mali                     |
| AU | Australia                | FR | France                                   | MN | Mongolia                 |
| BB | Barbados                 | GA | Gabon                                    | MR | Mauritania               |
| BE | Belgium                  | GB | United Kingdom                           | MW | Malawi                   |
| BF | Burkina Faso             | GN | Guinea                                   | NL | Netherlands              |
| BG | Bulgaria                 | GR | Greece                                   | NO | Norway                   |
| BJ | Benin                    | HU | Hungary                                  | PL | Poland                   |
| BR | Brazil                   | IE | Ireland                                  | RO | Romania                  |
| CA | Canada                   | IT | Italy                                    | RU | Russian Federation       |
| CF | Central African Republic | JP | Japan                                    | SD | Sudan                    |
| CG | Congo                    | KP | Democratic People's Republic<br>of Korea | SE | Sweden                   |
| CH | Switzerland              | KR | Republic of Korea                        | SN | Senegal                  |
| CI | Côte d'Ivoire            | LI | Liechtenstein                            | SU | Soviet Union             |
| CM | Cameroon                 | LK | Sri Lanka                                | TD | Chad                     |
| CS | Czechoslovakia           | LU | Luxembourg                               | TC | Togo                     |
| DE | Germany                  | MC | Monaco                                   | US | United States of America |
| DK | Denmark                  | MG | Madagascar                               |    |                          |
| ES | Spain                    |    |  |    |                          |

5

1

10

## METHOD AND APPARATUS FOR TREATING TISSUE

### 15      **Field of the Invention**

20                      This invention relates to a novel method and apparatus for treating tissue, including the application of an electric field to tissue surfaces as well as the delivery of topical drugs to an area of tissue to be treated using such electric field. More specifically, the invention relates to methods of delivering topical drugs, including proteins and nucleic acids, to skin by electrically stimulating the skin. Further, the invention relates to the transdermal delivery of electrical stimulation across the skin boundary to treat the underlying

25                      tissue. Such treatment can include the delivery of a drug or other compound to such tissue.

### **Background**

30                      Iontophoresis is a well known technique for delivering drugs through the skin which involves applying an electric potential gradient at the skin surface to enhance the permeability of the skin to the drug molecules. Research has been conducted on iontophoretic transdermal delivery of

peptide and protein drugs (Chien, Yie W., et al., (1989) J. of Pharm. Sci. 78, 376-383); nonpeptide drugs (Sanderson, et al., (1989) J. of Pharm. Sci. 78, 361-364); and polypeptide drugs (Srinivasan, V., et al., (1989) J. of Pharm. Sci. 78, 370-375).

5                   Iontophoresis has proven effective for  
transdermal delivery of local anesthesia, metallic and  
nonmetallic ions, vasodilators, dermatological medications,  
and steroids (Behl, et al. (1989) J. of Pharm. Sci. 78, 355-  
360). One of the earliest uses of iontophoresis involved  
10                introducing a sweat-inducing drug through the skin to  
diagnose cystic fibrosis (Chien, Yie W., et al. (1989) J. of  
Pharm. Sci. 78, 353-354). Other biomedical applications of  
iontophoresis include treatment for hyperhidrosis, edema  
formation, calcium deposits, and hay fever (Behl, et al.,  
15                (1989) J. of Pharm. Sci. 78, 355-360).

                  An iontophoretic drug delivery system generally  
includes a power source, control circuitry, and two electrode  
pads. One of the electrode pads contains a solution of an ionic  
drug and the other electrode pad contains an electrolyte. To  
20                effect delivery of the drug, the electrode pads are placed on  
the skin, and an electric current is supplied to the pads to  
induce an electric field at the skin surface. The power supply  
is connected to the electrode pads so that the charge of the pole  
connected to the drug-containing electrode is the same as the  
25                charge of the ionic drug. The application of an electric  
potential at the drug-containing electrode will drive the drug  
ions through the skin and into the body (Sanderson, John E. et  
al. (1987) J. of Pharm. Sci. 76, 215-218; Phipps, J. B., et al.  
(1989) J. of Pharm. Sci. 78, 365-369).

30                One such iontophoretic drug delivery system,  
marketed by Iomed, Inc. under the trademark TransQl,  
includes a dispersive electrode and a drug delivery electrode.  
The drug delivery electrode is mounted to a plastic holding

tray which includes an absorbent pad for receiving the drug. Once the pad is fully hydrated with the drug, the drug delivery electrode and absorbent pad are separated from the holding tray and placed on the skin at the treatment site. The  
5       dispersive electrode is placed on the skin spaced from the drug delivery electrode, and leads are attached to the pair of electrodes to generate an electric potential gradient at the treatment site. This drug delivery system is primarily used to deliver a water soluble medication, such as a local anesthetic  
10       and/or corticosteroid, through a patient's skin. A disadvantage of this system is the excessive length of time required for treatment.

Rogaine (Minoxidil, 2% topical solution) is a topically applied drug, marketed by the Upjohn Company,  
15       which has proven effective in treating male pattern baldness involving the top, or vertex, of the head. Although Rogaine has successfully stimulated hair growth on the top of the head, no clinically significant effect has been seen in patients with predominantly frontal hair loss.

20       Accordingly, it is therefore a general object of the invention to provide methods of treating the surface of tissue with an electric field.

It is a specific object of the invention to provide methods of applying a topical drug to a tissue which increases  
25       the efficiency and effectiveness of the drug.

It is a further specific object of the invention to provide a method of applying Rogaine to the frontal lobes of a user's head which stimulates detectable hair growth.

It is another object of the invention to provide an  
30       electrode device for use with the subject method which is sterile, disposable, noninvasive, pain free, easy to manufacture, and inexpensive to mass produce.

## Disclosure of the Invention

5 A preferred method of delivering topical drugs to the skin which is intended to accomplish at least some of the foregoing objects includes the step of applying the drug to be delivered to one of an area of skin to be treated and an electrode device. In a preferred embodiment, the drug is applied to the electrode device. The electrode device, which is formed to generate a multiplicity of simultaneous and directionally distinct electrical fields, is then placed in contact with the area of skin to be treated. Finally, voltage is delivered to the electrode device to generate simultaneous and directionally distinct electric fields at the skin surface.

15 Such methods and apparatus may be readily applied to similar treatment of other tissue surfaces. Further, such methods and apparatus may be readily adapted to apply unique electric fields to the surface of tissue and to tissue underlying such tissue surfaces to enhance circulation or the delivery of drugs to such tissue.

20

## Brief Description of the Drawings

25 Other objects and advantages of the present invention will become apparent from the following detailed description of a preferred embodiment thereof taken in conjunction with the accompanying drawings, wherein:

FIGURE 1 is a top plan view of an electrode device for use with the subject method of delivering topical drugs to the skin;

30 FIGURE 2 is an enlarged top view of a section of the electrode device of Figure 1; and

FIGURES 3a-c are photographs of enhanced hair growth using the methods and apparatus of the invention.

### Best Mode of Carrying Out the Invention

5           Before describing the subject methods of applying novel electric fields and the delivery of drugs to a tissue surface or underlying tissue, it may be helpful to describe the electrode device for use with the subject method. Referring to the drawings, wherein like numerals indicate like parts, and  
10           initially to FIGURE 1, there will be seen an electrode device 10 including a substantially planar support member 12 composed of a substantially non-conductive material. This device in general is made of a flexible planar support member to accommodate the contours of the tissue surface to be  
15           treated. Suitable non-conductive materials for forming support member 12 include mica, polyester, and polystyrene. Support member 12 has a main portion 14, preferably circular in shape, and a tab portion 16 extending from the perimeter of main portion 14. Tab portion 16 facilitates connection of lead  
20           lines to electrode device 10.

          A first electrode pattern 18a and a second electrode pattern 18b are disposed on main portion 14 of electrode device 10. First electrode pattern 18a and second electrode pattern 18b each include a set of substantially  
25           parallel electrodes 20a and 20b, respectively, which extend across main portion 14 in an alternating arrangement. Electrodes 20a and 20b are uniformly spaced across main portion 14 to ensure an even distribution of current density beneath electrode device 10, thereby reducing the likelihood of  
30           skin burns.

          A pair of electrode leads 22a and 22b extend along opposite sides of tab portion 16 and halfway around the

perimeter of main portion 14. Electrodes 20a are electrically coupled together by electrode lead 22a, and electrodes 20b are electrically interconnected by electrode lead 22b. Each set of electrodes 20a and 20b are electrically connected to one another so that a voltage applied to the corresponding electrode leads 22a and 22b is uniformly distributed across each of the electrodes.

The alternating arrangement of first and second electrode patterns 18a and 18b, respectively, generates multiple directionally distinct electrical fields when opposite charges are applied to electrode leads 22a and 22b. Turning to FIGURE 2, the arrows represent electric field lines generated by connecting lead lines of opposite polarity to electrode leads 22a and 22b.

Although a preferred embodiment of support member 12 is circular in shape, support member 12 may be fabricated in different shapes according to the area of tissue to be treated and according to the specific medical application.

Electrode patterns may be formed by screen printing a conductive ink on support member 12. A technique for printing a conductive ink on a flexible substrate is disclosed by M. Martel in "The Basics of Area Source IR", SITE Magazine, pgs. 60-64. Suitable conductive inks for forming the electrode patterns of the subject invention include E-1400 ink marketed by Ercon Incorporated and Electrodag PTF inks marketed by Acheson Colloids Company.

Alternatively, the electrode patterns may be formed by selectively depositing a metallic material, such as aluminum, on main portion 14. Or, the electrode patterns may be formed by using a masking technique to deposit copper vapor or other metallic vapor such as aluminum, gold, platinum, and nickel, on main portion 14.



The methods used to produce such vapor deposited electrode devices and selectively etched electrode devices are well known. Metal deposition may be carried out according to the methods disclosed by P. Gise and R. Blanchard in "Modern Semiconductor Fabrication Technology", Chapter 8 (Prentice-Hall, Englewood Cliffs, New Jersey, 1986), and A.B. Glaser and G.E. Subak-Sharpe in "Integrated Circuit Engineering", Chapter 5 (Addison-Wesley, Reading, Massachusetts, 1977) and selective etching of laminated material may be carried out according to the methods disclosed by C.F. Coombs, Jr., ed., in "Printed Circuit Handbook", Chapters 1 and 8 (McGraw-Hill, New York, New York, 1976).

The electrode material preferably ranges in thickness from approximately .001 inches to 1 inch. Each electrode has a width of approximately 10 $\mu$ m to 2mm, preferably between 0.1mm and 1mm. The spacing between the electrodes ranges from approximately 10 $\mu$ m to 2mm, preferably 0.1mm to 1mm.

Since these electrodes are positioned close together, a user may apply a relatively low voltage across first and second electrode leads 22a and 22b to generate an appropriate voltage gradient or sufficient electrical current. In most applications, 10 to 100 volts DC are applied across electrode leads 22a and 22b; however, the applied voltage may range from approximately 1 to 500 volts DC. It is preferable to deliver a pulsed voltage, as opposed to a continuous voltage, to electrode device 10 to prevent the build-up of charge on the skin.

The subject method for delivering a topical drug to tissue will now be described. According to the subject method, a topical drug is applied to one of an area of tissue to be treated and electrode device 10. Tissue includes but is not

limited to skin, tendons, muscles, nerves, internal organs and tissues of the oral cavity. In a preferred embodiment, the drug is applied to a localized area of skin to ensure even distribution of the drug across the skin surface. If the drug is applied directly to electrode device 10, the drug should be spread evenly across the surface of device 10 on which electrode patterns 18a and 18b are disposed, or the conductive surface of device 10. Once the drug has been applied, the conductive surface of device 10 is placed in contact with the area of skin to be treated. A voltage is then applied across electrode leads 22a and 22b to generate simultaneous and directionally distinct electric fields between electrodes 20a and 20b. The electric fields electrically stimulate the area of skin being treated. Although the exact mechanism is unknown, it is believed that application of electric fields to the skin surface enhances the permeability of the skin to the topical drug, thereby increasing the absorption of the drug through the skin. The increased absorption contributes to an increase in the efficiency and effectiveness of the drug delivery.

The subject method of the invention may be used in combination with the topical hair growth drug Rogaine, commercially marketed by The Upjohn Company. Previously, Rogaine has only been successful in promoting hair growth on the vertex of the head. However, when used in combination with electrode device 10, Rogaine has been shown to stimulate hair growth on the front of the scalp. According to the subject method, a user applies a full dose of Rogaine, specifically 1mL, to the front of the scalp per the directions found in the literature accompanying a Rogaine prescription. After the full dose has been applied to the user's scalp with the supplied rub-ON applicator, the user places the conductive surface of electrode device 10 in contact with the area of the scalp to be treated. The user then turns on the power supply to electrode device 10 which is preferably set to deliver approximately fifty to one hundred 100 volt DC pulses of 1 ampere of

current over a period of 15 to 30 seconds, each pulse lasting approximately 1 to 10 msec. As the pulses are being applied to electrode device 10, the user may move electrode device 10 over the area of skin being treated. The user may selectively  
5 apply pressure to electrode device 10 to adjust the contact of electrode device 10 with the skin. During treatment, the user may feel a sensation of mild tingling. After approximately four months of treatment, hair growth becomes apparent. This was repeated twice daily over 60 days.

10 The results of applying Rogaine to the frontal lobe of the scalp and treating the scalp with the electrode device as described above over a 60 day period are shown in FIGURES 3a-c. FIGURE 3a shows the condition of the scalp on day 0 prior to the start of the experiment. FIGURES 3b  
15 and 3c show the same scalp after 20 and 60 days, respectively. The right side of the scalp (left side in the figures) is the area treated with Rogaine and the electrode device 10. The left side of the scalp (right side in the figures) is the control area, i.e., treated only with Rogaine. In FIGURE 3b, new hair growth is  
20 seen at 20 days. As is also apparent in FIGURE 3c, hair growth after just 60 days was substantial.

The subject electrode device 10 may also be used in combination with other topical drugs to treat a variety of skin maladies including: (i) Retin A (Tretinoin, all, trans  
25 Retinoic Acid), commercially marketed by Ortho Pharmaceuticals, for treatment of brown spots, acne, and wrinkles, (ii) steroids to treat inflammation and psoriasis, (iii) topical pain relievers for treatment of aberrations of the skin and underlying tissue, and (iv) 5-fluorouracil to treat skin  
30 cancer and psoriasis.

In addition to delivering drugs to a localized area of skin and skin tissue, electrode device 10 may also be used without an accompanying topical drug. Electrical stimulation

alone has therapeutic and diagnostic value. Electrode device 10 may be used to electrically stimulate the skin of a user to, for example, increase blood flow, induce secretions, and stimulate nerves.

5                   As an example, tests were performed where the electrode device 10 was applied to the inner forearm area of a human. The same protocol as previously described was used except no topical drug was applied to the skin or electrode device 10. The test produced a region of redness indicating  
10                   increased circulation to the area. The increased circulation is useful for enhancing the delivery of drugs to the localized skin area which are administered IV or orally.

                  An advantage of using the apparatus and method of the invention lies in the fact that treatment can be effected  
15                   without significant discomfort of tissue damage (even after twice daily treatment for almost six months). The only feeling sensed by the user is a mere tingling of the scalp which is believed to be evidence of subcutaneous nerve stimulation.

                  Electrode device 10 may also provide gene  
20                   therapy to skin or other tissue by transfecting nucleic acid into the cells of the skin or tissue or cells underlying such surfaces for treating gene deficiencies or inducing such deficiencies in laboratory animals. Nucleic acids which may be used for transfection include DNA capable of expressing an antisense  
25                   RNA transcript which is capable of down modulating translation of endogenous RNA transcripts. Proteinaceous gene products may also be delivered to the skin cells by the subject method. Such proteins include Factor VIII, insulin, and adenosine deaminase.

30                   In describing the invention, reference has been made to a preferred embodiment and illustrative advantages of the invention. Those skilled in the art, however, and familiar with the instant disclosure of the subject invention, will

recognize additions, deletions, modifications, substitutions, and other changes which will fall within the purview of the subject invention and claims.

**CLAIMS**

What is claimed is:

- 5           1.    A method for delivering topical drugs to tissue comprising the steps of:  
              applying the drug to be delivered to one of an area of tissue to be treated and an electrode device formed to generate a multiplicity of simultaneous and directionally  
10           distinct electric fields;  
              placing said electrode device in contact with the area of tissue to be treated; and  
              delivering voltage to said electrode device to generate a multiplicity of directionally distinct electrical fields  
15           at the tissue surface to electrically stimulate the area of tissue being treated.
2.    A method as defined in claim 1 wherein:  
                  said electrode device includes a flexible,  
20           nonconductive, substantially planar support member; and  
                  first electrode means and second electrode means each including at least two electrically connected, substantially parallel electrodes, said first electrode means and said second electrode means arranged on a planar surface of said electrode  
25           device so that the electrodes of said first electrode means alternate with the electrodes of said second electrode means and, upon connection to said power supply, said electrode device generates said multiplicity of directionally distinct electric fields between the electrodes of said first electrode  
30           means and the electrodes of said second electrode means.
3.    A method as defined in claim 1 wherein:  
                  said applying step is accomplished by coating the area of tissue being treated with the drug.

4. A method as defined in claim 1 further comprising the step of:

after delivering said step, moving said electrode device over the area of tissue being treated.

5

5. A method as defined in claim 1 further comprising the step of:

after said delivering step, applying selective pressure to said electrode device to adjust contact of said electrode device with the area of tissue being treated.

10

6. A method as defined in claim 1 wherein:

said delivering step is accomplished by connecting a power supply to said electrode device to deliver a pulsed voltage to said electrode device.

15

7. A method as defined in claim 6 wherein:

said power supply delivers approximately 50 to 100 voltage pulses over approximately 15 to 30 seconds to said electrode device.

20

8. A method as defined in claim 7 wherein:

said power supply is set to deliver voltage pulses of approximately 100 volts at about 1 ampere, each having a duration approximately 1 to 10 msec.

25

9. A method as defined in claim 1 wherein:

said delivering step is accomplished by connecting a power supply to said electrode device to deliver a continuous voltage to said electrode device.

30

10. A method as defined in claim 1 wherein:

said electrode device is formed in the shape of the area of tissue to be treated.

35

11. A method as defined in claim 2 wherein:  
said second electrode means are formed by  
conductive inks.

5 12. A method of providing electrical stimulation to  
tissue comprising the steps of:

placing an electrode device in contact with the  
tissue, said electrode device formed to generate a multiplicity  
of directionally distinct electric fields, and delivering voltage  
10 to said electrode device to generate a multiplicity of  
simultaneous and directionally distinct electric fields at the  
tissue surface to electrically stimulate the tissue.

13. A method as recited in claim 12, wherein said  
15 tissue stimulated by said electrode device is skin.

14. A method of stimulating hair growth on the head  
of a user comprising the steps of:

20 applying a hair growth drug to an area of skin to  
be treated;

placing an electrode device in contact with the  
area of skin to be treated, said electrode device formed to  
generate a multiplicity of simultaneous and directionally  
distinct electric fields; and

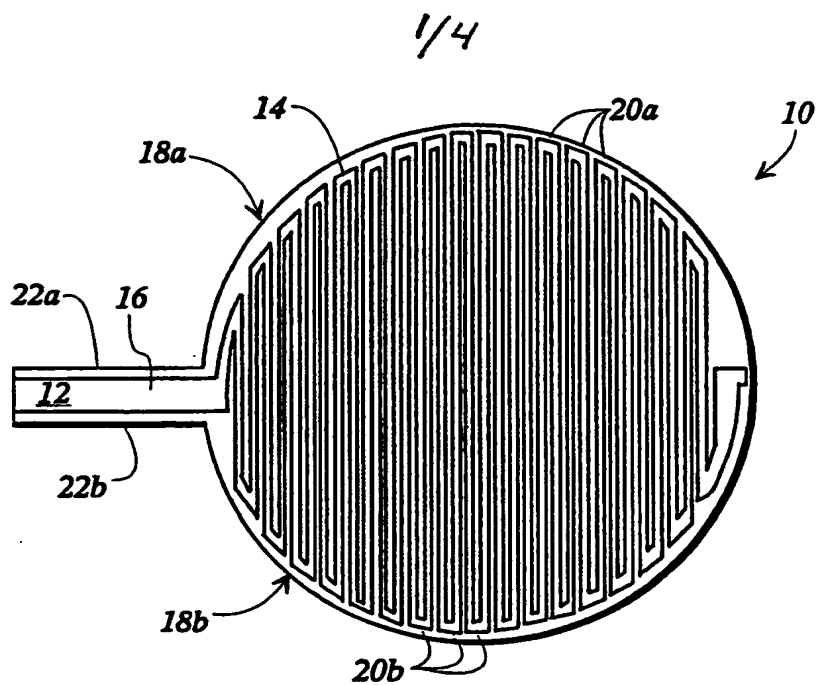
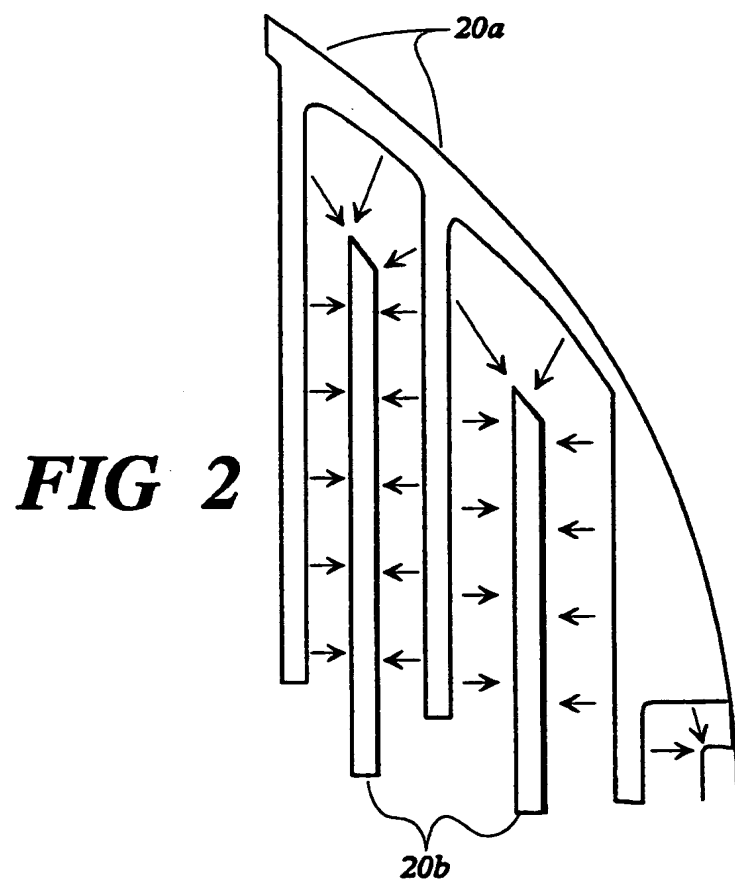
25 delivering voltage to said electrode device to  
generate a multiplicity of directionally distinct electric fields at  
the skin surface to electrically stimulate the area of skin being  
treated.

30 15. A method as defined in claim 14 wherein:  
said applying step is accomplished by spraying  
said hair growth drug on the frontal portion of a user's head.



16. A method as defined in claim 14 wherein:  
said applying step is accomplished by rubbing said  
hair growth drug on the frontal portion of a user's head.

5           17. An electrical stimulation apparatus comprising:  
a substantially planar support member having a  
substantially non-conductive surface, in contact with a tissue  
surface;  
first electrode means comprising at least two  
10 electrically-connected substantially parallel electrodes disposed  
on said substantially non-conductive surface; and  
second electrode means comprising at least two  
electrically-connected substantially parallel electrodes also  
disposed on the same surface as said first electrode means such  
15 that the electrodes of said first and second electrode means are  
alternately positioned on said surface.

**FIG 1****FIG 2**

2/4



**FIGURE 3A**

**DAY 0**

**SUBSTITUTE SHEET**

3/4



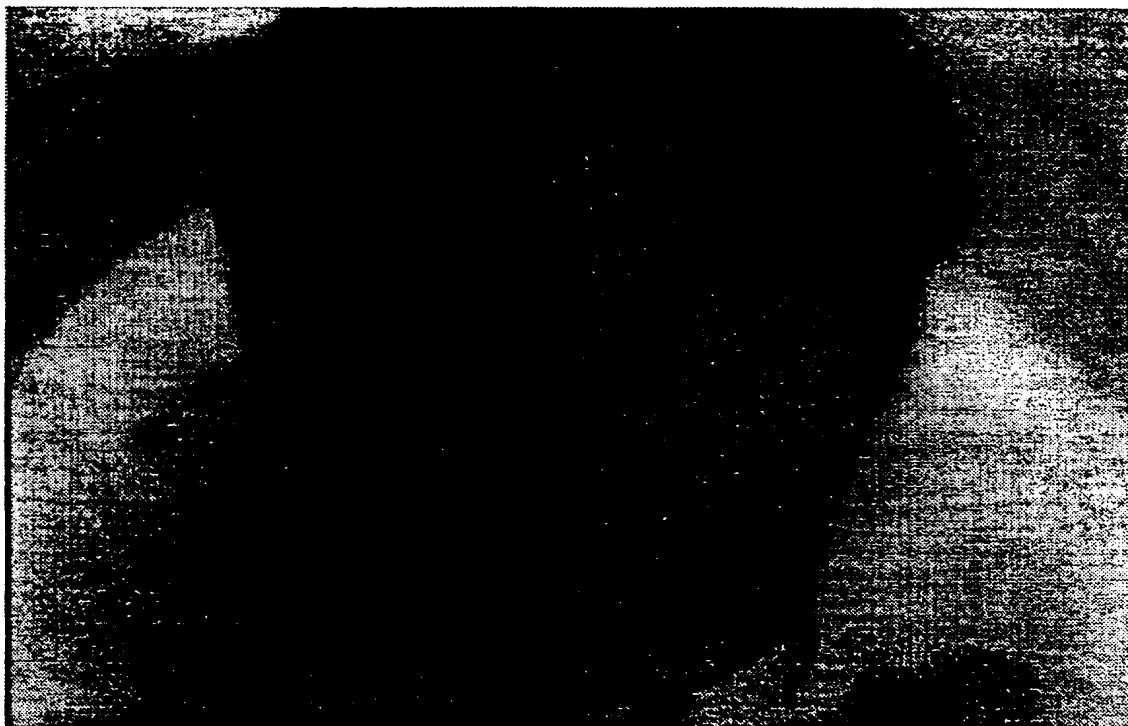
**FIGURE 3B**

**DAY 20**

**SUBSTITUTE SHEET**

414

12 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100



**FIGURE 3C**

**DAY 60**

**SUBSTITUTE SHEET**

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US92/05587

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(5) :A61N 1/30

US CL :604/20

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/798,799,802,803

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category*     | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No.         |
|---------------|--|-------------------------------|
| <u>X</u><br>Y | US, A, 4,164,226 (TAPPER) 14 August 1979, See figure 4.                            | <u>12,13,17</u><br>1-11,14-16 |
| Y             | US, A, 4,736,752 (MUNCK ET AL.) 12 April 1988, See Abstract.                       | 11                            |
| X             | US, A, 5,002,527 (RELLER ET AL.) 26 March 1991, See Abstract, Figure 1.            | 1,2,6,9                       |
| Y             | GB, A, 2,132,892 (HAYASHIBARA) July 1984, See Abstract.                            | 14-16                         |
| Y             | DE, A, 3,736,072 (COHAUSZ ET AL.) 13 April 1989.                                   | 1-11                          |

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

## \* Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be part of particular relevance

\*E\* earlier document published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\*

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\*

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\*

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

\*Z\*

document member of the same patent family

Date of the actual completion of the international search

17 AUGUST 1992

Date of mailing of the international search report

20 OCT 1992

Name and mailing address of the ISA/  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. NOT APPLICABLE

Authorized officer

MICHAEL RAFA

Telephone No. (703) 308-0858